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## Discovering NF- $\kappa$ B

David Baltimore

*Cold Spring Harb Perspect Biol* 2009;1:a000026

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## Discovering NF- $\kappa$ B

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NF- $\kappa$ B is a protein transcription factor that can orchestrate complex biological processes, such as the inflammatory response. It was discovered in a very different and very limited context, and only over time has its protean nature become evident.

It was actually a very logical process that led us to NF- $\kappa$ B. Although the discovery was very exciting, NF- $\kappa$ B was not the protein we were seeking at the time. To explain this, I must go back to when my laboratory first became interested in immunology.

My first independent position was at the Salk Institute, where I arrived in the spring of 1965. For the previous 4 years that I had been in research, my interests had revolved around the biochemistry of viruses. At Salk, although my work continued to be on viruses, I was exposed to the fascinating questions of immunology. The main issue was how the enormous diversity of antibodies is generated from a limited amount of genetic information. Like so many others, I thought about the question, but it took the experimental attention of Susumu Tonegawa, in 1976, to crack the problem and show that the solution involved DNA rearrangement.

In 1974, the methods of recombinant DNA technology were first developed and it was clear that previously intractable complex systems, like the immune system, could be examined with these methods. In 1976, knowing that the

methods were available and that the paradigm of DNA rearrangement had been established, some postdoctoral students in my laboratory and I decided to plunge into this field. I wanted to apply our biochemical skills to this suddenly tractable system. We were already working on one enzyme that was involved in immunoglobulin gene specification, terminal transferase, and had a useful viral transformation system in the laboratory that affected lymphoid cells, the Abelson mouse leukemia virus. So, immunology was not totally new to us.

We had to develop our skills with recombinant DNA methods, become familiar with the awful lingo of immunology, and define some questions for ourselves, but all of that came to pass. In time, I began to see the question of how immune cells develop as the key one for my laboratory. It seemed likely that the problem would come down to understanding the control of transcription factors. So, we focused on transcription of immune cell genes as our primary interest. We had produced evidence that in the development of B lymphocytes, the heavy-chain locus is first to rearrange its DNA, followed by the light-chain locus (Siden et al. 1981). Cary Queen joined the laboratory and studied the transcription of the  $\kappa$  light-chain gene and demonstrated that it contains an intragenic transcriptional enhancer (Queen and Baltimore 1983). These

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Editors: Louis M. Staudt and Michael Karin

Additional Perspectives on NF- $\kappa$ B available at [www.cshperspectives.org](http://www.cshperspectives.org)

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Cite this article as *Cold Spring Harb Perspect Biol* 2009;1:a000026

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developments led us to ask whether it might be possible to understand the transition of a cell from heavy-chain only to heavy-plus-light chain by understanding the transcription factors that bind to the  $\kappa$  light-chain enhancer. Understanding the proteins that bind to the regulatory sites in both the heavy- and the light-chain genes became the project of a new postdoctorate, Ranjan Sen. He worked closely with people in Phil Sharp's laboratory, who had similar interests.

Ranjan and Harinder Singh, from the Sharp laboratory, worked out how to use mobility shift assays to find transcription factors, and first published on the existence of the Oct factors (Singh et al. 1986). Then Ranjan applied the methods to enhancers and found multiple factors binding to both the heavy- and  $\kappa$  light-chain enhancers (Sen and Baltimore 1986a). Among the factors he discovered was one that bound only to the  $\kappa$  light-chain enhancer—it covered the sequence GGGACTTTCC. We called it NF- $\kappa$ B because it was a nuclear factor that bound selectively to the  $\kappa$  enhancer and was found in extracts of B-cell tumors but not other cell lines (Sen and Baltimore 1986a).

The next step was supposed to be the killer experiment. 70Z/3 cells were known to have a rearranged  $\kappa$  light chain but not to express it and did not have detectable NF- $\kappa$ B. We knew also that treatment of the cells with lipopolysaccharide (LPS) induced transcription of the  $\kappa$  gene. The killer result would be that LPS induced NF- $\kappa$ B. Sure enough, it did (Sen and Baltimore 1986b). Furthermore, it did so without the need for new protein synthesis. Thus, we concluded that NF- $\kappa$ B is a factor that pre-exists in an apparently inhibited state and is released from that inhibition by LPS treatment. It looked like we had found a factor that might cause cells to go from making only heavy chain to making heavy and light chains, which could thus explain a step in differentiation. However, history has treated this optimistic conclusion with total disrespect, as is shown below.

I will not describe all that we have done on the NF- $\kappa$ B system but will only take this story one step further. That step was taken by Patrick Baeuerle, who joined my laboratory as

a postdoctoral fellow. He found that the inactive form of NF- $\kappa$ B is in the cytoplasm of 70Z/3 cells and can be liberated from its inhibited form by treatment of cytoplasmic extracts with a detergent (Baeuerle and Baltimore 1988a). This discovery allowed us to purify the inhibitor, which we named I $\kappa$ B (Baeuerle and Baltimore 1988b). That set the stage for a detailed biochemical study of the activation process, an effort that has involved many investigators and is not complete to this day.

The seeds of doubt about the role of NF- $\kappa$ B as a regulator of B-cell development were sown in these early papers. We showed that the inhibited NF- $\kappa$ B is not specific to B-lineage cells: it was evident in T cells and even HeLa cells (Sen and Baltimore 1988b)—we know now that virtually all cells have it. Another paper showed this even more directly (Baeuerle and Baltimore 1988a). Thus, it was evident that NF- $\kappa$ B could be active in a wide range of cells and further work has borne this out.

A later postdoctorate, Yang Xu, provided the *coup de grace* for the notion that NF- $\kappa$ B is critical to  $\kappa$ -chain transcription. He knocked out the intronic  $\kappa$  enhancer—containing the NF- $\kappa$ B binding site—in mice and showed that, in those cells that rearrange  $\kappa$ , the gene is transcribed at a normal rate (Xu et al. 1996). There is a second enhancer, lacking an NF- $\kappa$ B binding site, that can control  $\kappa$  gene transcription. Each enhancer plays a quantitative role in  $\kappa$ -gene rearrangement, but not a qualitative one (Inlay et al. 2002).

Meanwhile, over the 24 years since its discovery, NF- $\kappa$ B has been implicated in a wide range of normal and disease processes. No transcription factor has attracted more experimental attention. Its role in inflammatory processes is especially important. Yet, its role in the transcription of the  $\kappa$  light chain, for which it was named, remains uncertain.

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